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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/424,629	03/13/2000	SIMON FOOTE	13203	8264

7590 09/29/2003

LEOPOLD PRESSER
SCULLY SCOTT MURPHY & PRESSER
400 GARDEN CITY PLAZA
GARDEN CITY, NY 11530

EXAMINER	
CHAKRABARTI, ARUN K	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 09/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/424,629	Simon Foote et al.
Examiner	**Art Unit**
Arun Chakrabarti	1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jul 28, 2003* .

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-18 and 24-35* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-18 and 24-35* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action*

DETAILED ACTION

Status of the application

1. Applicant's amendment filed on July 28, 2003, has been entered. Claims 1, 10, and 24 have been amended. New claims 33-35 have been added. Claims 1-18 and 24-35 are pending in this application.

Claim Rejections - 35 USC § 102

2. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

3. Claims 1, 3-5, 24-28, 33, and 35 are rejected under 35 U.S.C. 102 (b) over Kimura et al. (U.S. Patent 4,862,358) (August 29, 1989).

Kimura et al. teaches a method of detecting a difference of one or more nucleotides between a nucleic acid molecule to be tested and a reference nucleic acid molecule and identifying a mutation (Abstract) , the method comprising:

subjecting the test nucleic acid molecule to single-base specific cleavage to generate oligonucleotide fragments (Claims 19 and 27 and Column 14, line 21 to Column 20, line 17);

separating the resulting oligonucleotide fragments based on a procedure equivalent to MALDI-TOF MS to produce a fingerprint of the oligonucleotide fragments comprising one or more peaks wherein a peak represents the mass of each fragment (Figures 10-12 and Column 16, lines 38-48) (this rejection is based on the fact that any process (electrophoresis as used by kimura et al.) which is able to produce a fingerprint of the oligonucleotide fragments comprising one or more peaks wherein a peak represents the mass of each fragment, is equivalent to MALDI-TOF MS) ; and

identifying an altered peak relative to a reference nucleic acid molecule subjected to the same procedure wherein the presence of an altered peak is indicative of a difference of one or more nucleotides in the tested nucleic acid molecule (Column 21, lines 33-43 and Figures 11-12).

Kimura et al inherently teaches a method wherein the base specific cleavage results in oligonucleotide fragments of from about 2 bases to about 1000 bases (Figures 10-12).

Claim Rejections - 35 USC § 103

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CAR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

5. Claim 2 is rejected under 35 U.S.C. 103 (a) over Kimura et al. (U.S. Patent 4,862,358) (August 29, 1989) in view of Kamb (U.S. Patent 5,869,242) (February 9, 1999).

Kimura et al teaches a method of claims 1, 3-5, 24-28, 33, and 35 as described above.

Kimura et al does not teach a method, wherein the nucleic acid molecule to be tested is amplified by a PCR prior to base specific cleavage.

Kamb teaches a method, wherein the nucleic acid molecule to be tested is amplified by a PCR prior to base specific cleavage (Column 4, lines 36-46 and Column 7, lines 39-54).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute a method, wherein the nucleic acid molecule to be tested is amplified by a PCR prior to base specific cleavage of Kamb into the method of sequencing DNA of Kimura et al., since Kamb states, "A preferred approach is to amplify then digest the nucleic acid and then analyze it (Abstract, last sentence)." An ordinary practitioner

would have been motivated to combine and substitute a method, wherein the nucleic acid molecule to be tested is amplified by a PCR prior to base specific cleavage of Kamb into the method of sequencing DNA of Kimura et al. in order to achieve the express advantages, as noted by Kamb, of DNA polymorphism detection which provides a preferred approach of to amplify then digest the nucleic acid and then analyze it.

6. Claims 6-7 and 29-30 are rejected under 35 U.S.C. 103 (a) over Kimura et al. (U.S. Patent 4,862,358) (August 29, 1989) in view of Sutherland et al. (U.S. Patent 5,985,619) (November 16, 1999).

Kimura et al. teaches the method of claims 1, 3-5, 24-28, 33, and 35 as described above.

Kimura et al. does not teach the method wherein the base specific cleavage is uracil specific and mediated by uracil-N-glycosylase.

Sutherland et al. teach the method wherein the base specific cleavage is uracil specific and mediated by uracil-N-glycosylase (Column 9, lines 4-29).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the uracil specific base cleavage mediated by uracil-N-glycosylase of Sutherland et al. into the mass spectrometry to assess DNA sequence polymorphisms of Kimura et al., since Sutherland et al. state, "The glycosylase useful in the present invention are those that specifically cleave unconventional bases, i.e., bases other than A,G,C or T in DNA and A,G,C and U in RNA. Glycosylases that specifically cleave unconventional bases such as N-& methylguanine, 3-methyladenosine, uracil and hypoxanthine

are known to one of ordinary skill in the art. Preferred glycosylases include uracil N-glycosylase (UNG), hypoxanthine-DNA glycosylase, and 3-methyladenine-DNA glycosylases I and II. The most preferred glycosylase in accordance with present invention is UNG. UNG is commercially available (Column 9, lines 4-19)." By employing scientific reasoning, an ordinary artisan would have combined and substituted the uracil specific base cleavage mediated by uracil-N-glycosylase of Sutherland et al. into the mass spectrometry to assess DNA sequence polymorphisms of Kimura et al. in order to improve the sequencing of nucleic acids containing unconventional bases. An ordinary practitioner would have been motivated to combine and substitute the uracil specific base cleavage mediated by uracil-N-glycosylase of Sutherland et al. into the mass spectrometry to assess DNA sequence polymorphisms of Kimura et al. in order to achieve the express advantages noted by Sutherland et al., of a preferred glycosylase UNG which is commercially available and useful to specifically cleave unconventional bases.

7. Claims 10, 14, and 34 are rejected under 35 U.S.C. 103 (a) over Kimura et al. (U.S. Patent 4,862,358) (August 29, 1989) in view of Koster (U.S. Patent 6,074,823) (June 13, 2000).

Kimura et al. teaches the method of claims 1, 3-5, 24-28, 33, and 35 as described above.

Kimura et al. does not teach the method of using a computer capable of controlling a method of detecting mutation by MALDI-TOF MS.

Koster teach the method of using a computer capable of controlling a method of detecting mutation by MALDI-TOF MS (Column 5, lines 22-35).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute a computer capable of controlling a method of detecting mutation by MALDI-TOF MS of Koster into the mass spectrometry to assess DNA sequence polymorphisms of Kimura et al., since Koster states, "An additional advantage of mass spectrometric sequencing is that the identified masses can be registered automatically by a computer and, by adding the time coordinate, automatically aligned to sequences. Since the sequences so determined are memorized (i.e., saved to disk or resident in the computer memory), appropriate existing computer programs operating in a multitasking environment can be searching in the "background" (i.e., during continuous generation of new sequence data by the exonuclease mass spectrometric sequencer) for overlaps and generate contiguous sequence information which, via a link to a sequence data bank, can be used in homology searches, etc (Column 5, lines 22-35)." By employing scientific reasoning, an ordinary artisan would have combined and substituted a computer capable of controlling a method of detecting mutation by MALDI-TOF MS of Koster into the mass spectrometry to assess DNA sequence polymorphisms of Kimura et al. in order to improve the sequencing of nucleic acids by automated procedures. An ordinary practitioner would have been motivated to combine and substitute a computer capable of controlling a method of detecting mutation by MALDI-TOF MS of Koster into the mass spectrometry to assess DNA sequence polymorphisms of Kimura et al. in order to achieve the express advantages noted by Koster, of mass spectrometric sequencing by which the identified masses can be registered automatically by a computer and, by adding the time coordinate, automatically aligned to

sequences and since the sequences so determined are memorized (i.e., saved to disk or resident in the computer memory), appropriate existing computer programs operating in a multitasking environment can be searching in the "background" (i.e., during continuous generation of new sequence data by the exonuclease mass spectrometric sequencer) for overlaps and generate contiguous sequence information which, via a link to a sequence data bank, can be used in homology searches, etc

8. Claims 8-9, 11-13, and 31-32 are rejected under 35 U.S.C. 103 (a) over Kimura et al. (U.S. Patent 4,862,358) (August 29, 1989) in view of Caprioli (U.S. Patent 5,808,300) (September 15, 1998).

Kimura et al. teaches the method of claims 1, 3-5, 24-28, 33, and 35 as described above.

Kimura et al. does not teach the method of subjecting fragmentation products to further separation by the post source decay method.

Caprioli teaches the method of subjecting fragmentation products to further separation by post source decay method (Column 3, lines 9-11).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute a further separation by post source decay method of Caprioli into the mass spectrometry to assess DNA sequence polymorphisms of Kimura et al. , since Caprioli states, "The use of post-source decay techniques is shown in order to obtain sequence verification (Column 3, lines 9-11)." By employing scientific reasoning, an ordinary artisan would have combined and substituted a further separation by post source decay

method of Caprioli into the mass spectrometry to assess DNA sequence polymorphisms of Kimura et al. in order to improve the sequencing of nucleic acids. An ordinary practitioner would have been motivated to combine and substitute a further separation by post source decay method of Caprioli into the mass spectrometry to assess DNA sequence polymorphisms of Kimura et al. in order to achieve the express advantages, as noted by Caprioli, of a method which is used in order to obtain sequence verification.

9. Claims 16 is rejected under 35 U.S.C. 103 (a) over Kimura et al. (U.S. Patent 4,862,358) (August 29, 1989) in view of Koster (U.S. Patent 6,074,823) (June 13, 2000) further in view of Sutherland et al. (U.S. Patent 5,985,619) (November 16, 1999).

Kimura et al. in view of Koster teach the method of claims 1, 3-5, 24-28, 33, and 35 as described above.

Kimura et al. in view of Koster do not teach the method wherein the base specific cleavage is uracil specific and mediated by uracil-N-glycosylase.

Sutherland et al. teach the method wherein the base specific cleavage is uracil specific and mediated by uracil-N-glycosylase (Column 9, lines 4-29).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the uracil specific base cleavage mediated by uracil-N-glycosylase of Sutherland et al. into the computerized mass spectrometry to assess DNA sequence polymorphisms of Kimura et al. in view of Koster, since Sutherland et al. state, "The glycosylase useful in the present invention are those that specifically cleave unconventional bases,

i.e., bases other than A,G,C or T in DNA and A,G,C and U in RNA. Glycosylases that specifically cleave unconventional bases such as N-& methylguanine, 3-methyladenosine, uracil and hypoxanthine are known to one of ordinary skill in the art. Preferred glycosylases include uracil N-glycosylase (UNG), hypoxanthine-DNA glycosylase, and 3-methyladenine-DNA glycosylases I and II. The most preferred glycosylase in accordance with present invention is UNG. UNG is commercially available (Column 9, lines 4-19)." By employing scientific reasoning, an ordinary artisan would have combined and substituted the uracil specific base cleavage mediated by uracil-N-glycosylase of Sutherland et al. into the computerized mass spectrometry to assess DNA sequence polymorphisms of Kimura et al. in view of Koster in order to improve the sequencing of nucleic acids containing unconventional bases. An ordinary practitioner would have been motivated to combine and substitute the uracil specific base cleavage mediated by uracil-N-glycosylase of Sutherland et al. into the computerized mass spectrometry to assess DNA sequence polymorphisms of Kimura et al. in view of Koster in order to achieve the express advantages noted by Sutherland et al., of a preferred glycosylase UNG which is commercially available and useful to specifically cleave unconventional bases.

10. Claims 15 is rejected under 35 U.S.C. 103 (a) over Kimura et al. (U.S. Patent 4,862,358) (August 29, 1989) in view of Caprioli (U.S. Patent 5,808,300) (September 15, 1998)further in view of Sutherland et al. (U.S. Patent 5,985,619) (November 16, 1999).

Kimura et al. in view of Caprioli teach the method of claims 1-5, 8-9, 11-13, 24-28, 31-32, 33, and 35 as described above.

Kimura et al. in view of Caprioli do not teach the method wherein the base specific cleavage is uracil specific and mediated by uracil-N-glycosylase.

Sutherland et al. teach the method wherein the base specific cleavage is uracil specific and mediated by uracil-N-glycosylase (Column 9, lines 4-29).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the uracil specific base cleavage mediated by uracil-N-glycosylase of Sutherland et al. into the computerized mass spectrometry to assess DNA sequence polymorphisms of Kimura et al. in view of Caprioli, since Sutherland et al. state, "The glycosylase useful in the present invention are those that specifically cleave unconventional bases, i.e., bases other than A,G,C or T in DNA and A,G,C and U in RNA. Glycosylases that specifically cleave unconventional bases such as N-& methylguanine, 3-methyladenosine, uracil and hypoxanthine are known to one of ordinary skill in the art. Preferred glycosylases include uracil N-glycosylase (UNG), hypoxanthine-DNA glycosylase, and 3-methyladenine-DNA glycosylases I and II. The most preferred glycosylase in accordance with present invention is UNG. UNG is commercially available (Column 9, lines 4-19)." By employing scientific reasoning, an ordinary artisan would have combined and substituted the uracil specific base cleavage mediated by uracil-N-glycosylase of Sutherland et al. into the mass spectrometry to assess DNA sequence polymorphisms of Kimura et al. in view of Caprioli in order to improve the sequencing of nucleic acids containing unconventional bases. An ordinary practitioner would have been motivated to combine and substitute the uracil specific base cleavage mediated by uracil-N-glycosylase of

Sutherland et al. into the computerized mass spectrometry to assess DNA sequence polymorphisms of Kimura et al. in view of Caprioli in order to achieve the express advantages noted by Sutherland et al., of a preferred glycosylase UNG which is commercially available and useful to specifically cleave unconventional bases.

11. Claims 17-18 are rejected under 35 U.S.C. 103 (a) over Kimura et al. (U.S. Patent 4,862,358) (August 29, 1989) in view of Koster (U.S. Patent 6,074,823) (June 13, 2000) further in view of Caprioli (U.S. Patent 5,808,300) (September 15, 1998).

Kimura et al. in view of Koster teach the method of claims 1-5, 10, 14 , 24-28, 33, and 35 as described above.

Kimura et al. in view of Koster do not teach the method of subjecting fragmentation products to further separation by the post source decay method.

Caprioli teaches the method of subjecting fragmentation products to further separation by post source decay method (Column 3, lines 9-11).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute a further separation by post source decay method of Caprioli into the computerized mass spectrometry to assess DNA sequence polymorphisms of Kimura et al. in view of Koster, since Caprioli states, "The use of post-source decay techniques is shown in order to obtain sequence verification (Column 3, lines 9-11)." By employing scientific reasoning, an ordinary artisan would have combined and substituted a further separation by post source decay method of Caprioli into the computerized mass spectrometry to

assess DNA sequence polymorphisms of Kimura et al. in view of Koster in order to improve the sequencing of nucleic acids. An ordinary practitioner would have been motivated to combine and substitute a further separation by post source decay method of Caprioli into the computerized mass spectrometry to assess DNA sequence polymorphisms of Kimura et al. in view of Koster in order to achieve the express advantages, as noted by Caprioli, of a method which is used in order to obtain sequence verification.

Response to Amendment

12. In response to amendment, all previous 102(e) as well as 103(a) rejections are hereby withdrawn. However, new 102(b) and 103(a) rejections are hereby included.

Response to Arguments

13. Applicant's arguments with respect to all pending claims have been considered but are moot in view of the new ground(s) of rejection.

Applicant is also hereby notified that although there was an interview on July 9, 2003 between the applicant and Examiner Arun Chakrabarti, and supervisor Gary Banzion and it was agreed to amend the claims to clarify the novelty of the invention, but the claims as amended are not persuasive for allowance because of the following reasons:

(1) Applicant claimed broadly MALDI-TOF MS or other equivalent procedure in the independent claims but the disclosure in the specification is limited only to MALDI-TOF MS and therefore the claims are not supported by the disclosure for enablement.

(2) The broad claims are also encompassed by the prior art reference Kimura et al. as mentioned above.

Conclusion

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Arun Chakrabarti, Ph.D., whose telephone number is (703)

306-5818. The examiner can normally be reached on 7:00 AM-4:30 PM from Monday to Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached on (703) 308-1119. The fax phone number for this Group is (703) 746-4979. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group analyst Chantae Dessau, who can be reached at (703) 605-1237.

Arun Chakrabarti,

Patent Examiner,

September 24, 2003

ARUN K. CHAKRABARTI
PATENT EXAMINER

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